

Studies and Synthesis of Biologically Active Mixed Ligand Cerium (III) Complexes

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Abstract: Mixed ligand complexes cerium(III) of the type $[M(Q)(L)\cdot 2H_2O]$ have been synthesized by using 8-hydroxy quinoline (HQ) as a primary ligand and N- and/or O- donor amino acids (HL) such as L-proline, L-valine and L-serine as secondary ligands. The metal complexes have been characterized by elemental analysis, electrical conductance, room temperature magnetic susceptibility measurements, spectral and thermal studies. The electrical conductance studies of the complexes indicate their non-electrolytic nature. Room temperature magnetic susceptibility measurements specify that cerium(III) complexes are paramagnetic in nature. Electronic absorption spectra of the complexes show intra-ligand, charge transfer and d-d transitions respectively. The thermal analysis data of the complexes indicates the presence of coordinated water molecules. FTIR spectra show bonding of the metal ion through N- and O- donor atoms of the ligand molecules. Tube dilution and Agar cup methods were implemented for study of antibacterial activity of the complexes against *S. aureus*, *C. diphtheriae*, *S. typhi* and *P. aeruginosa*. The tetracycline is used as standard antibacterial compound to study the antibacterial study of the synthesized complexes and it was found that, the complexes show mild activity against selected strains of micro-organisms as compared to standard tetracycline.

Keywords: mixed ligand cerium complexes, synthesis, characterization and biological studies.

1. Introduction

Literature survey exhibited that many researchers have studied characterization and biological study of mixed ligand complexes of transition metals [1]-[6]. Mixed ligand complexes play a vital role in biological process [7], [8]. These metal complexes with 8-hydroxyquinoline exhibited biological activity [9]-[11]. Mixed ligand complexes are formed with amino acids which are well known for their biological significance and metabolic enzymatic activities [12]. Mixed ligand complexes of Ce(III) showed the antifungal activity [13]-[14]. These complexes also characterize for their cytotoxic activity [15].

The author therefore thought to undertake the study of mixed ligand complexes of cerium, with 8-hydroxy quinoline (HQ) as a primary ligand and different amino acids (HL) such as, L-proline, L-valine and L-serine as secondary ligands. The metal complexes have been characterized by elemental analysis and various physico-chemical techniques such as molar conductance, magnetic susceptibility, electronic spectra, IR spectra and thermal studies.

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2. Experimental

2.1 Materials

Cerium(III) chloride heptahydrate of analytical grade was used as such without purification. Amino acids, L-proline, L-valine and L-serine were obtained from E. Merck. Solvents like DMF and DMSO whenever used were distilled and purified according to standard procedures [16]-[18].

2.2 Preparation of mixed ligand complexes

The mixed ligand cerium(III) complexes were prepared from cerium chloride heptahydrate with primary ligand (HQ) and L-proline, L-valine and L-serine as secondary ligands (HL) in 1:2:1 proportion. To an aqueous solution (10 ml) of cerium(III) chloride heptahydrate (372 mg, 1mmol), ethanolic solution (20 ml) of 8-hydroxy quinoline (290 mg, 2mmol) was added. The mixture was stirred and kept in a boiling water bath for 10 minutes. To this hot solution, an aqueous solution (10 ml) of amino acids (1 mmol) was added with constant stirring. The mixture was again heated in a water bath till the temperature reached to 50°C. The complexes were precipitated by raising pH of the reaction mixture by adding diluted ammonia solution. The mixture was cooled and solid complex obtained was filtered, washed with water followed by ethanol. The complexes thus prepared were dried under vacuum and were used for further studies.

2.3 Instrumentation

The synthesized cerium(III) complexes were analyzed for C, H, and N contents on Thermo Finnigan Elemental Analyzer Model no. FLASH EA 1112 Series at the Department of Chemistry, I.I.T., Mumbai. Metal content was estimated gravimetrically by standard procedure [19], [20]. The molar

conductance values were measured in DMF (10^{-3} M) on an Equipronics Autoranging Conductivity Meter Model No. EQ-667. Room temperature magnetic susceptibilities were measured by a Guoy method using $\text{Hg}[\text{Co}(\text{SCN})_4]$ as a calibrant at the Department of Chemistry, I.I.T., Mumbai. The electronic absorption spectra of all the complexes in DMF solution (10^{-4} M) in the ultraviolet and visible region were recorded on Shimadzu UV/VIS-160 Spectrophotometer. FT-IR spectra were recorded in KBr disc on a Perkin-Elmer FT-IR spectrophotometer Model 1600 at Department of Chemistry, I.I.T., Mumbai. Thermal Analysis (TG and DTA) were carried out in controlled nitrogen atmosphere on a Perkin-Elmer Diamond TG-DTA Instrument Department of Chemistry, I.I.T., Mumbai by recording the change in weight of the complexes on increasing temperature up to 900°C at the heating rate of 10°C per minute.

2.4 Antibacterial Screening

2.4.1 Agar Cup Method

In this method, a single compound can be tested against number of organisms or a given organism against different concentrations of the same compound. It was found suitable for semisolid or liquid samples and was used in the present work.

In agar cup method, a plate of sterile nutrient agar with the desired test strain was poured to a height of about 5mm, allowed to solidify and a single cup of 8 mm diameter was cut from the center of the plate with a sterile cork borer. Thereafter the cup was filled with the sample solution of $1000 \mu\text{g}/\text{cm}^3$ concentration. The test solution was allowed to diffuse in surrounding agar by keeping in refrigerator for 10 min and the plate was incubated at 37°C for 24 hrs. The extent of inhibition of growth from the edge of the cup was considered as a measure of the activity of the given compound. By using several plates simultaneously, the activities of several samples could be qualitatively studied.

2.4.2 Tube dilution method

The test compounds were subjected to *in vitro* screening against *Staphylococcus aureus*, *Corynebacterium diphtheriae*, *Salmonella typhi* and *P. aeruginosa* using Muller Hinton broth as the culture medium.

The test compound (10 mg) was dissolved in DMSO (10 cm^3) so as to prepare a stock solution of concentration $1000 \mu\text{g}/\text{cm}^3$. From this stock solution, aliquots of 5, 10, 15, 20 to , $250 \mu\text{g}/\text{cm}^3$ were obtained in test broth. Bacterial inoculums were prepared in sterilized Muller Hinton broth and incubated for 24 hrs. at 37°C . The aliquots were dispensed (5 cm^3) in each borosilicate test tube (150 x 20 mm). The bacterial inoculums 0.1 cm^3 of the desired bacterial strain (*S. aureus*, *C. diphtheriae*, *S. typhi* and *P. aeruginosa*) containing 10^6 bacteria/ cm^3 was inoculated in the tube. The tubes were incubated at 37°C for 24 hrs. and then examined for the presence or absence of the growth of the test organisms.

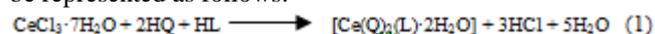
The lowest concentration which showed no visible growth was noted as minimum inhibitory concentration (MIC). Tetracycline was used as standard drug against Gram-

positive and Gram-negative bacteria by similar screening procedure. The solvent DMSO was also tested as control to see that it did not affect the growth of the culture. MIC of tetracycline was found to be $1.5 \mu\text{g}/\text{cm}^3$ against *S. aureus*, $2.0 \mu\text{g}/\text{cm}^3$ against *C. diphtheriae*, $1.5 \mu\text{g}/\text{cm}^3$ against *S. typhi* and $8.0 \mu\text{g}/\text{cm}^3$ against *P. aeruginosa*.

3. Results and Discussion

3.1 Characterization of metal complexes

The synthesis of mixed ligand cerium (III) complexes may be represented as follows:



(Where, HQ is 8-hydroxy quinoline and HL is an amino acid)

All the complexes are coloured, non-hygroscopic and thermally stable solids (Table 1 and 2), indicating a strong metal-ligand bond. The complexes are insoluble in common organic solvents such as ethyl alcohol, acetone, etc. but are partially soluble in DMF and DMSO. The elemental analysis data (Table 3) of metal complexes is consistent with their general formulation as 1:2:1, mixed ligand complexes of the type $[\text{Ce}(\text{Q})_2(\text{L}) \cdot 2\text{H}_2\text{O}]$. The molar conductance values of the complexes in DMF at 10^{-3} M concentration are found to be $0.0019-0.0023 \text{ mhos cm}^2 \text{ mol}^{-1}$ indicating their non-electrolytic nature [21].

Table 1: Empirical Formula, Molecular Weight and Colour

Complex	Empirical Formula	Molecular Weight	Colour
$[\text{Ce}(\text{Q})_2(\text{Pro}) \cdot 2\text{H}_2\text{O}]$	$\text{CeC}_{23}\text{H}_{24}\text{O}_6\text{N}_3$	578.57	Brown
$[\text{Ce}(\text{Q})_2(\text{Val}) \cdot 2\text{H}_2\text{O}]$	$\text{CeC}_{23}\text{H}_{26}\text{O}_6\text{N}_3$	580.59	Brown
$[\text{Ce}(\text{Q})_2(\text{Ser}) \cdot 2\text{H}_2\text{O}]$	$\text{CeC}_{21}\text{H}_{22}\text{O}_7\text{N}_3$	568.53	Brown

Table 2: Decomposition Temperature and pH

Complex	Decomposition Temperature ($^\circ\text{C}$)	pH
$[\text{Ce}(\text{Q})_2(\text{Pro}) \cdot 2\text{H}_2\text{O}]$	235	7.01
$[\text{Ce}(\text{Q})_2(\text{Val}) \cdot 2\text{H}_2\text{O}]$	240	7.05
$[\text{Ce}(\text{Q})_2(\text{Ser}) \cdot 2\text{H}_2\text{O}]$	230	6.99

Where, Q represents the deprotonated primary ligand 8-hydroxy quinoline whereas Pro, Val and Ser represent deprotonated secondary ligands, L-proline, L-valine and L-serine respectively.

Table 3: Elemental Analysis Data and Molar Conductance of Cerium Complexes

Complex	Elemental Analysis Found (Calculated)				Molar Conductance ($\text{Mhos cm}^2 \text{ mol}^{-1}$)
	%M	%C	%H	%N	
$[\text{Ce}(\text{Q})_2(\text{Pro}) \cdot 2\text{H}_2\text{O}]$	24.23 (24.22)	47.77 (47.75)	04.20 (04.18)	07.29 (07.26)	0.0019
$[\text{Ce}(\text{Q})_2(\text{Val}) \cdot 2\text{H}_2\text{O}]$	24.17 (24.13)	47.61 (47.58)	04.55 (04.51)	07.28 (07.24)	0.0023
$[\text{Ce}(\text{Q})_2(\text{Ser}) \cdot 2\text{H}_2\text{O}]$	24.66 (24.65)	44.3 (44.36)	03.90 (03.90)	07.42 (07.39)	0.0022

3.2 Magnetic Studies

The magnetic moment of the mixed ligand cerium(III) complexes (Table 4) were calculated from the measured magnetic susceptibilities after employing diamagnetic corrections and revealed their paramagnetic nature [22]-[23].

Table 4: Magnetic susceptibility data of Cerium complexes (-10^{-6} c.g.s. units)

Complex	X_g	X_m	μ_{eff} (B.M.)
[Ce(Q) ₂ (Pro)·2H ₂ O]	-2.43×10^{-6}	1.40×10^{-3}	1.95
[Ce(Q) ₂ (Val)·2H ₂ O]	-2.26×10^{-6}	1.32×10^{-3}	1.89
[Ce(Q) ₂ (Ser)·2H ₂ O]	-2.01×10^{-6}	1.14×10^{-3}	1.77

3.3 Electronic Absorption Spectra

The electronic spectra of the metal complexes in DMF were recorded in the UV-visible region (Table 5). The spectra show three transitions in the range 273-278 nm ($35971-36630 \text{ cm}^{-1}$), 336-338 nm ($28586-29762 \text{ cm}^{-1}$) and 395-396 nm ($25253-25316 \text{ cm}^{-1}$) ascribed to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and charge transfer transitions from the ligands to the metal respectively [24].

Table 5: Electronic Spectral data of Cerium complexes

Complex	λ (nm)	ν (cm^{-1})	Proposed Assignments
[Ce(Q) ₂ (Pro)·2H ₂ O]	276	36232	$\pi \rightarrow \pi^*$
	337	29674	$n \rightarrow \pi^*$
	395	25316	Charge-transfer
[Ce(Q) ₂ (Val)·2H ₂ O]	278	35971	$\pi \rightarrow \pi^*$
	336	29762	$n \rightarrow \pi^*$
	396	25253	Charge-transfer
[Ce(Q) ₂ (Ser)·2H ₂ O]	273	36630	$\pi \rightarrow \pi^*$
	338	29586	$n \rightarrow \pi^*$
	395	25316	Charge-transfer

3.4 Infra-red spectra

The FTIR spectra of the metal complexes were recorded in KBr discs over the range $4000-400 \text{ cm}^{-1}$. These spectra were complex due to presence of numerous bands with varying intensities, making the task quite difficult. However, an attempt has been made to assign some of the important bands on the basis of reported infrared spectra of several N and / or O donor ligands, 8-hydroxy quinoline and their metal complexes. An important feature of infrared spectra of the metal complexes is the absence of band at $\sim 3440 \text{ cm}^{-1}$ due to the O-H stretching vibration of the free O-H group of HQ. This observation leads to the conclusion that complex formation takes place by deprotonation of the hydroxyl group of HQ moiety. A strong $\nu(\text{CO})$ band observed in the range of $1110-1105 \text{ cm}^{-1}$ in the spectra of the complexes, indicates the presence of the 8-hydroxyquinolate group in the complexes co-ordinating through its nitrogen and oxygen atoms as uninegative bidentate ligand. The $\nu(\text{C}=\text{N})$ mode observed at 1580 cm^{-1} in the spectrum of free HQ ligand is found to be shifted to lower wave at 1503 cm^{-1} in the spectra of the complexes, suggesting co-ordination through the tertiary nitrogen donor of HQ. The in-plane and out-of-plane deformation modes observed at $\sim 500 \text{ cm}^{-1}$ and $\sim 780 \text{ cm}^{-1}$ respectively, in the spectrum of HQ are shifted to higher wave numbers 504 cm^{-1} and 790 cm^{-1} respectively,

confirming co-ordination through the nitrogen atom of HQ with the metal ion.

A broad band observed in the region between $3210-3207 \text{ cm}^{-1}$ due to asymmetric and symmetric O-H stretching modes and a weak band in the range of $1577-1575 \text{ cm}^{-1}$ due to H-O-H bending vibrations indicating presence of a coordinated water molecule [25]-[27], further confirmed by thermal studies. The N-H asymmetric and N-H symmetric vibrations observed at ~ 3042 and $\sim 2965 \text{ cm}^{-1}$, respectively, in the free amino acids are shifted to higher wave numbers i.e. in the range $3178-3082 \text{ cm}^{-1}$ and $3055-3050 \text{ cm}^{-1}$, respectively, in the spectra of the complexes, suggesting co-ordination of the amino group through nitrogen with the metal ion. The $\nu_{\text{asymmetric}}(\text{COO}^-)$ band of the free amino acids i.e. $\sim 1590 \text{ cm}^{-1}$ is shifted to higher wave number, i.e. in the range $1639-1633 \text{ cm}^{-1}$ and the $\nu_{\text{symmetric}}(\text{COO}^-)$ mode observed at $\sim 1400 \text{ cm}^{-1}$ in the spectra of free amino acids is found to be shifted to lower wave number in the range of $1377-1372 \text{ cm}^{-1}$, in the spectra of complexes indicating the co-ordination of the carboxylic acid group via oxygen with the metal ion. Coordination through the amino group of the amino acids has been further confirmed by the C-N symmetrical stretching frequency. It is observed at $\sim 950 \text{ cm}^{-1}$ in the spectra of free amino acids and found to be shifted to lower wave numbers 912 cm^{-1} in the spectra of the complexes. Some new bands of weak intensity observed in the regions around $605-600 \text{ cm}^{-1}$ and 409 cm^{-1} may be ascribed to the M-O and M-N vibrations respectively. It may be noted that these vibrational bands are absent in the infra-red spectra of HQ as well as amino acids.

3.5 Thermal studies

The TG and DTA studies of the complexes have been recorded in the nitrogen atmosphere at the constant heating rate of $10 \text{ }^\circ\text{C} / \text{minute}$. Thermal study on mixed ligand cerium complexes in controlled nitrogen atmosphere was carried out to understand stages of decomposition and temperature range of decomposition.

The most probable decomposition pattern of the complexes is proposed on the basis of the careful examination of TG and DTA curves. The thermo analytical data is summarized in (Table 6,7 and 8).

The TG of the complexes shows that, they are thermally quite stable to varying degree. The complexes show gradual loss in weight due to decomposition by fragmentation with increasing temperature. The complexes L-proline, L-valine and L-serine show similar behaviour in TG and DTA studies. The thermogram of these complexes shows the loss in weight corresponding to two water molecules in the temperature range $125-160^\circ\text{C}$, followed by weight loss due to amino acid moiety in the temperature range $230-410^\circ\text{C}$. The final step of decomposition observed in the temperature range $615-835^\circ\text{C}$ corresponds to two molecules of 8-hydroxyquinoline in the complex.

Thermal decomposition of all the cerium(III) complexes in inert atmosphere produces finely divided metal powder which gets transformed to their oxides spontaneously even in the presence of traces of oxygen present in nitrogen gas used

in the experiment. The constant weight plateau in TG of cerium(III) after 835°C indicates completion of the reaction.

Table 6: Thermal Data of Cerium Complexes showing % Loss due to Water Molecules

Sr. No.	Complex	% Weight Loss due to Water Molecules		
		Temperature Range (°C)	Found	Calculated
1	[Ce(Q) ₂ (Pro)·2H ₂ O]	125-155	6.25	6.22
2	[Ce(Q) ₂ (Val)·2H ₂ O]	130-160	6.28	6.20
3	[Ce(Q) ₂ (Ser)·2H ₂ O]	135-160	6.48	6.33

Table 7: Thermal Data of Cerium Complexes showing % Loss due to Amino Acid

Sr. No.	Complex	% Weight Loss due to Amino Acid		
		Temperature Range (°C)	Found	Calculated
1	[Ce(Q) ₂ (Pro)·2H ₂ O]	235-410	19.78	19.73
2	[Ce(Q) ₂ (Val)·2H ₂ O]	240-400	20.00	20.01
3	[Ce(Q) ₂ (Ser)·2H ₂ O]	230-410	18.45	18.31

Table 8: Thermal Data of Cerium Complexes showing % Loss due to 8HQ Molecules

Sr. No.	Complex	% Weight Loss due to 8HQ Molecules		
		Temperature Range (°C)	Found	Calculated
1	[Ce(Q) ₂ (Pro)·2H ₂ O]	630-810	49.95	49.83
2	[Ce(Q) ₂ (Val)·2H ₂ O]	620-830	49.72	49.66
3	[Ce(Q) ₂ (Ser)·2H ₂ O]	615-835	50.79	50.71

On the basis of the physicochemical studies, the bonding and structure for the cerium complexes may be represented as. +

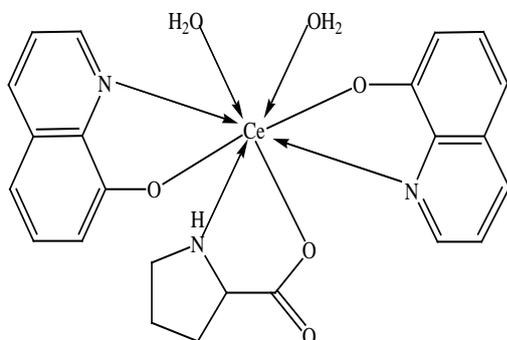


Figure 1: Proposed Structures of [Ce(Q)₂(Pro)·2H₂O]

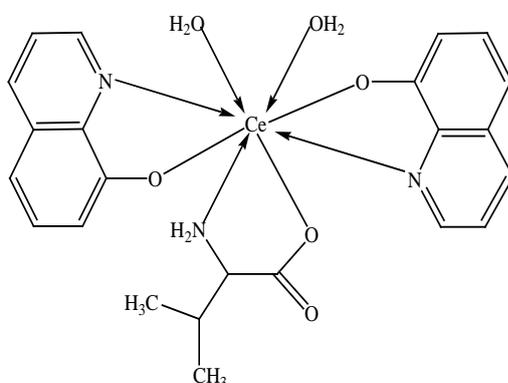


Figure 2: Proposed Structures of [Ce(Q)₂(Val)·2H₂O]

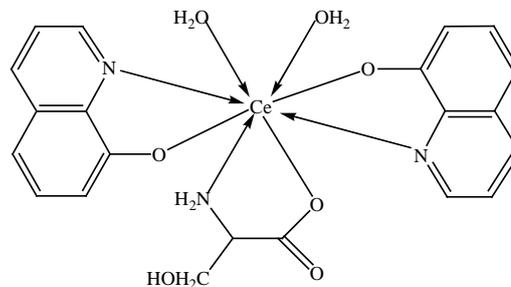


Figure 3: Proposed Structures of [Ce(Q)₂(Ser)·2H₂O]

3.6 Biological studies

All the metal complexes were screened against *Staphylococcus aureus*, *Corynebacterium diphtheriae*, *Salmonella typhi* and *P. aeruginosa*.

The studies based on agar cup method revealed that the complexes are more sensitive against *S. aureus* and *S. typhi* while less sensitive against *C. diphtheria* and *P. aeruginosa* (Table 9).

The minimum inhibitory concentration (MIC) of ligand and the metal salts ranges between 50 and 300 µg/mL while that of metal complexes ranges between 5 and 35 µg/mL (Table 10). The complexes are found to be more active against *S. aureus* and *S. typhi* compared to *C. diphtheria* and *P. aeruginosa*. As compared to standard antibacterial compound tetracycline, the complexes show moderate activity against selected strains of microorganisms.

The results show that, as compared to the activity of metal salts and free ligand, the metal complexes show higher activity [28]. The activity of metal complexes is enhanced due to chelation. The chelation reduces considerably the polarity of the metal ions in the complexes, which in turn increases the hydrophobic character of the chelate and thus enables its permeation through the lipid layer of microorganisms [29].

Table 9: Antibacterial Activity (mm) of Cerium Complexes by Agar Cup Method

Complex	Antibacterial Activity (mm) with			
	<i>S. aureus</i>	<i>C. diphtheriae</i>	<i>S. typhi</i>	<i>p. aeruginosa</i>
[Ce(Q) ₂ (Pro)·2H ₂ O]	26	18	20	11
[Ce(Q) ₂ (Val)·2H ₂ O]	28	17	22	13
[Ce(Q) ₂ (Ser)·2H ₂ O]	28	15	21	14

Table 10: MIC (µg/mL) Data of Cerium Complexes

Complex	MIC (µg/mL)			
	<i>S. aureus</i>	<i>C. diphtheriae</i>	<i>S. typhi</i>	<i>p. aeruginosa</i>
[Ce(Q) ₂ (Pro)·2H ₂ O]	15	25	15	30
[Ce(Q) ₂ (Val)·2H ₂ O]	10	20	20	25
[Ce(Q) ₂ (Ser)·2H ₂ O]	10	25	15	35
8-hydroxyquinoline	50	200	150	250
Tetracycline	1.5	2.0	1.5	8.0

4. Conclusions

On the basis of above observations, following conclusions are made. The higher decomposition temperatures of the complexes indicate a strong metal-ligand bond and electrical

conductance studies show non-electrolytic nature of the complexes, respectively. Magnetic studies indicate paramagnetic nature of the complexes. Electronic absorption spectra of the complexes show intra ligand and charge transfer transitions, respectively. IR spectra show bonding of the metal ion through N- and O-donor atoms of the two ligands. Thermal analysis confirms the presence of two coordinated water molecules. On the basis of the above results, coordination number eight is proposed for cerium complexes. The antibacterial study shows that complexes are found to be more active against *S. aureus* and *S. typhi* as compared to *C. diphtheria* and *P. aeruginosa*. Compared to standard antibacterial compound, tetracycline, the complexes show mild activity against the selected strains of microorganisms.

5. Future Scope

The current study can be beneficial in medicinal field by studying biological activities of these complexes.

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